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| EXAMINER | |
|---|---|
| HURT, SHARON L | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/620,787 | SIMARD ET AL. | |
| | Examiner | Art Unit | |
| | SHARON HURT | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-10,12-17 and 20-31* is/are pending in the application.

4a) Of the above claim(s) *3-6 and 12-17* is/are withdrawn from consideration.

5)☒ Claim(s) *9 and 31* is/are allowed.

6)☒ Claim(s) *1-2, 7-8, 10 and 20-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Amendment*

The amendments to the claims filed December 18, 2008 have been acknowledged and entered. Claim 31 is currently amended.

The amendments to the specification have been acknowledged and entered.

The amendments to the drawings, Fig. 9, has been acknowledged and entered.

### *Status of the Claims*

Claims 1-10, 12-17 and 20-31 are pending. Claims 3-6 and 12-17 have been withdrawn from consideration. Claims 1-2, 7-10 and 20-31 are under examination.

### *Claim Objections*

The objection of claim 31 because the claim does not have a sequence identifier for polyprotein LAA is withdrawn. Claim 31 has been amended to incorporate the sequence identifier.

### *Rejections Maintained*

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

**Claims 1-2, 7-8, 10, 20, 22 and 27-30 stand** rejected under 35 U.S.C. 103(a) as being unpatentable over Hooper et al. (Virology, 2000, Vol. 266, pages 329-339) in view of Hooper et al. (US 2002/0009447 A1).

The claimed invention is drawn to an immunogenic composition comprising a polyprotein or a polyprotein comprising external immunogens of membrane-associated proteins of variola major, vaccinia virus or immunologically cross-reactive poxviruses, wherein each of said external immunogens comprise a portion of said membrane-associated protein comprising the external epitopes, wherein at least two of the poxvirus membrane-associated proteins are selected from the group consisting of: M1R, A36R, I5R, B7R, F8L, A30L, A33R, H5R, B5R, D8L, and A27L, wherein the antibodies against one of the proteins are synergistic with antibodies against one other protein; wherein the synergistic antibodies recognize A36R of variola major or A33R of vaccinia, wherein the complex is formed by anchoring the polypeptides in a liposome or micelle.

The claimed invention is also drawn to a method of making an immunogen and an immunogenic composition comprising a cocktail of immunogens and a method of making the cocktail.

Hooper et al. (hereinafter Hooper) teaches a DNA vaccine comprising the vaccinia virus L1R and A33R genes (Abstract and page 332). The combined construct was used to vaccinate mice to see if the mice were protected against lethal challenge (page 332). The plasmid DNA was transfected using Lipofectin, a liposome (page 338, 1st full paragraph).

Hooper et al. Publication (US 2002/0009447 A1) (hereinafter Hooper Pub) teaches about vaccinia virus and variola virus and a live virus vaccine to prevent disease (paragraphs 002-003). Hooper Pub teaches a composition of one or more vaccinia antigens which are used to elicit antibodies in mice and are defined to be important for protection (paragraph 005). Hooper Pub teaches that one neutralizing monoclonal antibody alone, i.e. antibodies raised against proteins

D8L or A27L, did not provide protection and that antibodies against two or more proteins, i.e. L1R and A33R, are required for protection (paragraphs 006-007). Hooper Pub also teach that L1R and A33R homologs from other poxvirus can be used as immunogens to produce monoclonal antibodies, which would most likely be protective since homologs in other poxviruses have high identity with the vaccinia virus proteins (paragraph 009). Therefore these surface proteins are synergistic with antibodies against at least one other protein. Hooper Pub teaches that monoclonal antibodies raised against L1R and A33R protect against vaccinia virus infection (paragraph 0009). Hooper Pub further teaches monoclonal antibodies raised against vaccinia antigens L1R, A33R, H3L, D8L, A27L and A17L (paragraph 0023).

Hooper Pub teaches active immunization can be induced by administering one or more antigenic and/or immunogenic epitopes as a component of a subunit vaccine (paragraph 0041). Hooper Pub teaches the host can be actively immunized with the antigenic/immunogenic peptide in pure form, a fragment of the peptide, or a modified for of the peptide (paragraph 0041). Hooper Pub also teaches amino acids useful for coupling the peptide to another peptide, to a large carrier protein, or to a support (paragraph 0041).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to recognize the synergy of antibodies against other proteins. The person of ordinary skill in the art would have been motivated to make that connection because Hooper Pub teaches homologs from other poxvirus can be used as immunogens to produce monoclonal antibodies, which would most likely be protective since homologs in other poxviruses have high identity with the vaccinia virus proteins, and reasonably would have expected success because of the teachings of Hooper and Hooper Pub.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to combine the proteins in the same vaccine because Hooper Pub teaches the proteins work together and that they can be combined in the same vaccine. The person of ordinary skill in the art would have been motivated to make a polyprotein because Hooper Pub teaches the proteins can be linked together in the same vaccine construct, and reasonably would have expected success because of the teachings of Hooper and Hooper Pub.

***Response to Arguments***

Applicant's arguments filed December 18, 2008 have been fully considered but they are not persuasive. Applicants argue "Neither Hooper nor Hooper Pub, individually or in combination, teach or suggest polyproteins". Applicants argue "Hooper teaches only naked DNA vaccines and does not teach or suggest complexes of proteins or polypeptides." Applicants argue "Hooper Pub does not cure the deficiencies of Hooper in that it also does not teach immunogenic compositions comprising complexes or polypeptides." Hooper Pub suggests linking proteins together in the same vaccine (paragraph 0041).

Applicants argue "Hooper teaches that when plasmids containing the L1R and A33R vaccinia genes are loaded onto the same gold particle, and therefore expressed in the same cell, immunization is ineffective for the generation of neutralizing antibodies or protection from viral challenge." Applicants argue "Therefore Hooper teaches away from the claimed invention". A freeze dried or liquid vaccine preparation would not be prepared on gold beads for use in a liquid injector. Therefore, the vaccine composition would not all be deposited in the same cell. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Hooper teaches combining L1R and A33R in a vaccine. Hooper Pub teaches the proteins can be fused together in the same vaccine. One of ordinary skill in the art would be motivated to combine the proteins into the same vaccine as illustrated in Hooper PUB. The combination of references teaches the instant invention.

Applicants argue "that Hooper and Hooper Pub, either singly or in combination, do not teach or suggest polyproteins or protein complexes comprising external immunogens of at least two membrane-associated proteins of variola major or immunologically cross-reactive poxviruses." Hooper teaches a vaccine comprising two membrane-associated proteins L1R and A33R. Hooper Pub suggests fusing the proteins together in the same vaccine composition.

With regard to the strict construction and application of the TSM test, Applicant is directed to KSR v. Teleflex, Inc., No. 04-1350 (U.S. Apr. 30, 2007), which states, "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." (KSR, slip op. at 14). The Court continued, stating that "helpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents. The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the

importance of published articles and the explicit content of issued patents." KSR, slip op. at 15. As such, the rejection at issue and its analysis under 103(a) meets all of the *prima facie* requirements under Graham v. Deere (1966) (*supra*) and KSR v. Teleflex (2007) (*supra*).

**Claim 21 stands** rejected under 35 U.S.C. 103(a) as being unpatentable over Hooper et al. (Virology, 2000, Vol. 266, pages 329-339) in view of Hooper et al. (US 2002/0009447 A1) as applied to claim 1-2, 7-8, 10, 20, 22 and 27-30 above, and further in view of Curiel et al. (6,274,332).

The claimed invention is drawn to the invention described above wherein the polypeptides are biotinylated and the complex is formed by the addition of avidin or streptavidin.

The teachings of Hooper are described above. Hooper does not teach biotinylation or the formation of a complex with avidin or streptavidin.

Curiel et al. (hereinafter Curiel) teaches conjugates which contain a virus, wherein binding of the virus is through a biotin-streptavidin bridge (column 17, lines 12-17). Curiel teaches that complexes consisting of DNA and streptavidin-protein, to which the biotin modified virus is bound, have a high transfection efficiency, even at lower concentrations of DNA. Curiel also notes that the binding to biotin may also be affected by means of avidin.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to have used a biotin-streptavidin bridge to make a conjugate of proteins from variola major and/or vaccinia. The person of ordinary skill in the art would have been motivated to make that (those) modification(s) because Curiel et al teach a high transfection

efficiency when proteins are conjugated via biotin-avidin, and reasonably would have expected success because of the teachings of Hooper and Curiel.

***Response to Arguments***

Applicant's arguments have been fully considered but they are not persuasive. Applicants argue "Curiel does not teach or suggest a polyprotein and therefore does not cure the deficiencies of Hooper and Hooper Pub." Applicants argue Hooper, Hooper Pub and Curiel, either singly or in combination, do not teach protein complexes comprising external immunogens of at least two membrane-associated proteins of variola major or immunologically cross-reactive poxviruses wherein the polypeptides are biotinylated and the complex is formed by the addition of streptavidin." As discussed above, Hooper teaches a vaccine comprising two membrane-associated proteins L1R and A33R. Hooper Pub suggests fusing the proteins together in the same vaccine composition. Curiel teaches conjugates which contain a virus, wherein binding of the virus is through a biotin-streptavidin bridge. The combination of references teaches the instant invention.

**Claims 23-26 stand** rejected under 35 U.S.C. 103(a) as being unpatentable over Hooper et al. as applied to claims 1-2, 7-8, 10, 20, 22 and 27-30 above, and further in view of Newton et al. (Biochemistry, 1996, Vol. 35, pages 545-553).

The claimed invention is drawn to the invention described above and a polyprotein comprising external immunogens of at least two membrane-associated proteins of variola major or immunologically cross-reactive poxviruses wherein the individual proteins are joined through a linker-spacer peptide and wherein each said external immunogen comprises a portion of said

membrane-associated protein comprising the external epitopes, wherein linker-spacer peptide comprises GGGGSSGG, and wherein the polyprotein further comprises an affinity tag (or specifically a poly-histidine tag).

The teachings of Hooper are described above. Hooper does not teach joining the proteins together with a linker or attaching an affinity tag.

Newton et al. (hereinafter Newton) teaches flexible peptide linkers used to join fusion proteins as Gly-Ser linkers $(GGGGS)_3$ (page 545, Abstract). Newton also teaches attaching a poly-histidine affinity tag to facilitate purification of the fusion proteins (page 546, second column).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to a flexible linker peptide (Gly-Ser) coding sequence as taught by Newton as an effective means of joining polypeptides together. One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have used the poly-histidine tag taught by Newton as an effective means to facilitate purification of the polyproteins. The person of ordinary skill in the art would have been motivated to make that (those) modification(s) because Newton teaches it is an effective means of joining polypeptide together, and reasonably would have expected success because of the teachings of Hooper and Newton.

***Response to Arguments***

Applicant's arguments have been fully considered but they are not persuasive. Applicants argue "Newton does not teach or suggest a polyprotein and therefore does not cure the deficiencies of Hooper and Hooper Pub." As discussed above, Hooper teaches a vaccine comprising two membrane-associated proteins L1R and A33R and Hooper Pub suggests fusing

the proteins together in the same vaccine composition. Therefore Hooper and Hooper Pub teach a polyprotein or more than one protein fused together in a vaccine composition.

***Conclusion***

Claims 9 and 31 are free of the prior art.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHARON HURT whose telephone number is 571-272-3334. The examiner can normally be reached on M-F 8:00 - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sharon Hurt

March 9, 2009
/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648